
The secondary heart field is a new site of calcineurin/Nfatc1 signaling for semilunar valve development.

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Public Summary:

This article describes how cardiac progenitor cells contribute to the development of heart valves.

Scientific Abstract:

Semilunar valve malformations are common human congenital heart defects. Bicuspid aortic valves occur in 2-3% of the population, and pulmonic valve stenosis constitutes 10% of all congenital heart disease in adults (Brickner et al., 2000) [1]. Semilunar valve defects cause valve regurgitation, stenosis, or calcification, leading to endocarditis or congestive heart failure. These complications often require prolonged medical treatment or surgical intervention. Despite the medical importance of valve disease, the regulatory pathways governing semilunar valve development are not entirely clear. In this report we investigated the spatiotemporal role of calcineurin/Nfatc1 signaling in semilunar valve development. We generated conditional knockout mice with calcineurin gene disrupted in various tissues during semilunar valve development. Our studies showed that calcineurin/Nfatc1 pathway signals in the secondary heart field (SHF) but not in the outflow tract myocardium or neural crest cells to regulate semilunar valve morphogenesis. Without SHF calcineurin/Nfatc1 signaling, the conal endocardial cushions--the site of prospective semilunar valve formation--first develop and then regress due to apoptosis, resulting in a striking phenotype with complete absence of the aortic and pulmonic valves, severe valve regurgitation, and perinatal lethality. This role of calcineurin/Nfatc1 signaling in the SHF is different from the requirement of calcineurin/Nfatc1 in the endocardium for semilunar valve formation (Chang et al., 2004) [2], indicating that calcineurin/Nfatc1 signals in multiple tissues to organize semilunar valve development. Also, our studies suggest distinct mechanisms of calcineurin/Nfat signaling for semilunar and atrioventricular valve morphogenesis. Therefore, we demonstrate a novel developmental mechanism in which calcineurin signals through Nfatc1 in the secondary heart field to promote semilunar valve morphogenesis, revealing a new supportive role of the secondary heart field for semilunar valve formation.

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